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Review

The immune system in the normal endometrium and implications for endometrial cancer development

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ABSTRACT

Although described for the first time some decades ago, the contribution of the immune system to the establishment of tumors has not been extensively pursued for a long time. Over the last decade, however, more and more evidence has been accumulating concerning the role the immune system plays in tumor development and progression and its possible role in patient prognosis. In addition, interest is growing in preclinical and clinical research concerning the use of the immune system in the treatment of cancer. Immunotherapy for gynecological cancers in general, and for endometrial cancer in particular, is still in its infancy. Only a small number of studies, with varying success rates, have been published. Here, we provide a concise overview of the literature available on the role of the immune system in the normal endometrium and in endometrial cancer, in addition to the possible implications for future immunotherapeutic studies.

1. Introduction

Many risk factors involved in the etiology of endometrial cancer have been described. Obesity and physical inactivity are two significant risk factors for the development of uterine tumors, along with elevated blood pressure, high energy intake, high serum glucose levels and increased exposure to estrogens (Amant et al., 2005). For some of these risk factors, the effects on and interactions with the immune system have been reported. Hormonal fluctuations during the menstrual cycle have been described to modulate immune functions, as reviewed by Wira et al. (2010). Hormonal fluctuations and interactions with immune cells result in a protective environment against invading pathogens, while creating a favorable environment for embryonic implantation and fetal development. Obesity, which is related to an increased risk of developing endometrial cancer, is considered to be a chronic inflammatory state, causing increased release of pro-inflammatory cytokines such as IL-6 and CRP (Visser et al., 1999).

In addition to the effect of the risk factors described on the immune system, the vast majority of endometrial cancer cases are diagnosed in post-menopausal women and often in elderly patients. Age has an important influence on the immune system, the so-called immunosenescence, which parallels hormonal changes that occur with increasing age (Pfister and Savino, 2008). Aging causes an overall

Abbreviations: BMI, body mass index; COX-2, cyclo-oxygenase 2; CRP, C-reactive protein; CTL, cytotoxic T lymphocyte; DC, dendritic cells; HLA-G, human leukocyte antigen G; IDO, indoleamine 2,3-dioxygenase; MALT, mucosa-associated lymphoid tissue; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGE2, prostaglandin E2; TDLN, tumor-draining lymph nodes; TAM, tumor-associated macrophages; Treg, regulatory T cells.

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decrease in immune-related functions and results in a latent pro-inflammatory state.

Taken together, these data indicate that risk factors associated with the occurrence of endometrial cancer have an important influence on the immune system. In the current review, we provide an overview of the role the immune system plays in the normal non-pregnant uterus and how changes in the immune system may play a role in the development of uterine tumors and the possible clinical outcome. This knowledge is important for successful further development of immunotherapeutic strategies for uterine cancer.

2. The uterine immune system under physiological conditions and in cancer

The immune system in the normal uterus serves a dual purpose. On the one hand, it plays a role in protection against pathogens, while on the other hand, it has the ability to adapt to an immunosuppressive state in order to create feto-maternal tolerance toward a semi-allogeneic fetus. These separate functions involve the complex interplay of the hormonal fluctuations of the menstrual cycle and the immune system. Normal endometrium is naturally under strict hormonal control. It is under constant control of the variations in estradiol and progesterone during the menstrual cycle. Both the innate and adaptive arms of the immune system are influenced by these hormonal changes. Several risk factors have been described for endometrial cancer, which may be linked to increased inflammation of the endometrial tissue, as reviewed by Modugno et al. (2005). Increased exposure to estrogens has been shown to be associated with endometrial cancer development, owing to the mitogenic effect of estrogens (Austin et al., 1991; Potischman et al., 1996; Zeleniuch-Jacquotte et al., 2001). Consequently, estrogen-related carcinogenesis may be related to inflammatory events. Chronic inflammation has been linked to cancer development (Hanahan and Weinberg, 2011). Several inflammation pathways are involved in carcinogenesis. Many of these pathways are initialized by, among others, activation of STAT 3 or NF-κB (Elinav et al., 2013). The detailed role these pathways and their downstream mediators play in carcinogenesis is beyond the scope of this review and is briefly summarized in Fig. 1. This interplay is discussed and further elaborated on by Elinav et al. (2013).

2.1. Immune functions of normal and malignant endometrial cells

The endometrial epithelium serves as the primary line of defense against viruses and other pathogens entering the uterus. The epithelial cells form an integral part of the mucosal immune system. Next to forming a physical barrier, the epithelial cells have several direct immune-related functions, one of which is the secretion of defensins (Wira et al., 2005b). Defensins form a part of the innate immune system, considering their immediate antimicrobial function and their ability to activate the adaptive immune system. For example, defensins have been shown to attract T cells and immature dendritic cells (DC) in response to binding to the C-C chemokine receptor type 6 (CCR6) (Yang et al., 1999). Other secreted molecules include macrophage inflammatory protein (MIP)3α, also a ligand for CCR6, and secretory leukocyte protease inhibitor (SLPI) (Fahey and Wira, 2002; Fahey et al., 2006a). In contrast, uterine epithelial cells secrete unidentified, soluble immune mediators that confer a tolerogenic phenotype to DC (Ochiel et al., 2010).

Obesity and diabetes have also been shown to be associated with increased release of pro-inflammatory molecules, such as IL-6, TNF-α, CRP, leptin, and macrophage migration inhibitory factor (Dandona et al., 2004; Visser et al., 1999). Two studies evaluating the serum levels of IL-6, TNF-α, and CRP, and the risk of developing endometrial cancer, have shown that elevated levels of CRP are associated with endometrial cancer risk (Friedenreich et al., 2013; Wang et al., 2011). Wang et al. (2011) found this correlation after correcting for BMI and age. Friedenreich et al. (2013), in addition, found that CRP and endometrial cancer risk were associated with high BMI, and that serum IL-6 and endometrial cancer risk were associated with low BMI.

Indoleamine 2,3-dioxygenase (IDO), which is responsible for T cell suppression through the deprivation of the crucial metabolite tryptophan, is up-regulated in secretory *versus* proliferative endometrium. The presence of the enzyme may play a dual protective role: it functions as an anti-bacterial agent and induces suppression of T cells. The latter creates an immunosuppressive state to allow embryonic implantation (Lobo et al., 2004). IDO is also expressed by endometrial carcinoma cells (de Jong et al., 2012; Ino et al., 2008; Vanderstraeten et al., 2014), and was proven to be associated with myometrial invasion, lymph node metastases and lymphovascular space involvement (Ino et al., 2008). In addition, high IDO expression correlated with decreased $CD8^+$ TIL and NK cell involvement and was associated with poor survival (de Jong et al., 2012). Thus, in both normal and malignant endometrium, the primary function of IDO seems to be the induction of immunosuppression in order to allow embryonic implantation or tumor growth.

Endometrial epithelial cells are also potent antigen-presenting cells. Ferguson et al. found expression of major histocompatibility complex (MHC) class I in endometrial glands and in stromal cells and endothelial cells. MHC class II, on the contrary, was found to be expressed in the endometrial glands in approximately 50% of normal endometrium samples (Ferguson et al., 1985). Fahey et al. have shown that cultured epithelial cells express CD40 and CD1d and that epithelial cells in addition to stromal endometrial cells can elicit tetanus toxoid-specific T cell responses (Fahey et al., 2006b; Wallace et al., 2001). In endometrial tumors, classical MHC class I was down-regulated in 48.5% of 520 tumors, which is associated with worse disease prognosis (Bijen et al., 2010). In addition, the non-classical MHC class I molecule, human leukocyte antigen G (HLA-G) was up-regulated in 39.8% of samples, corroborating the results of Barrier et al., who found expression of HLA-G in 55% of samples (Barrier et al., 2006). Although requiring further investigation, the up-regulation of HLA-G molecules in endometrial tumors

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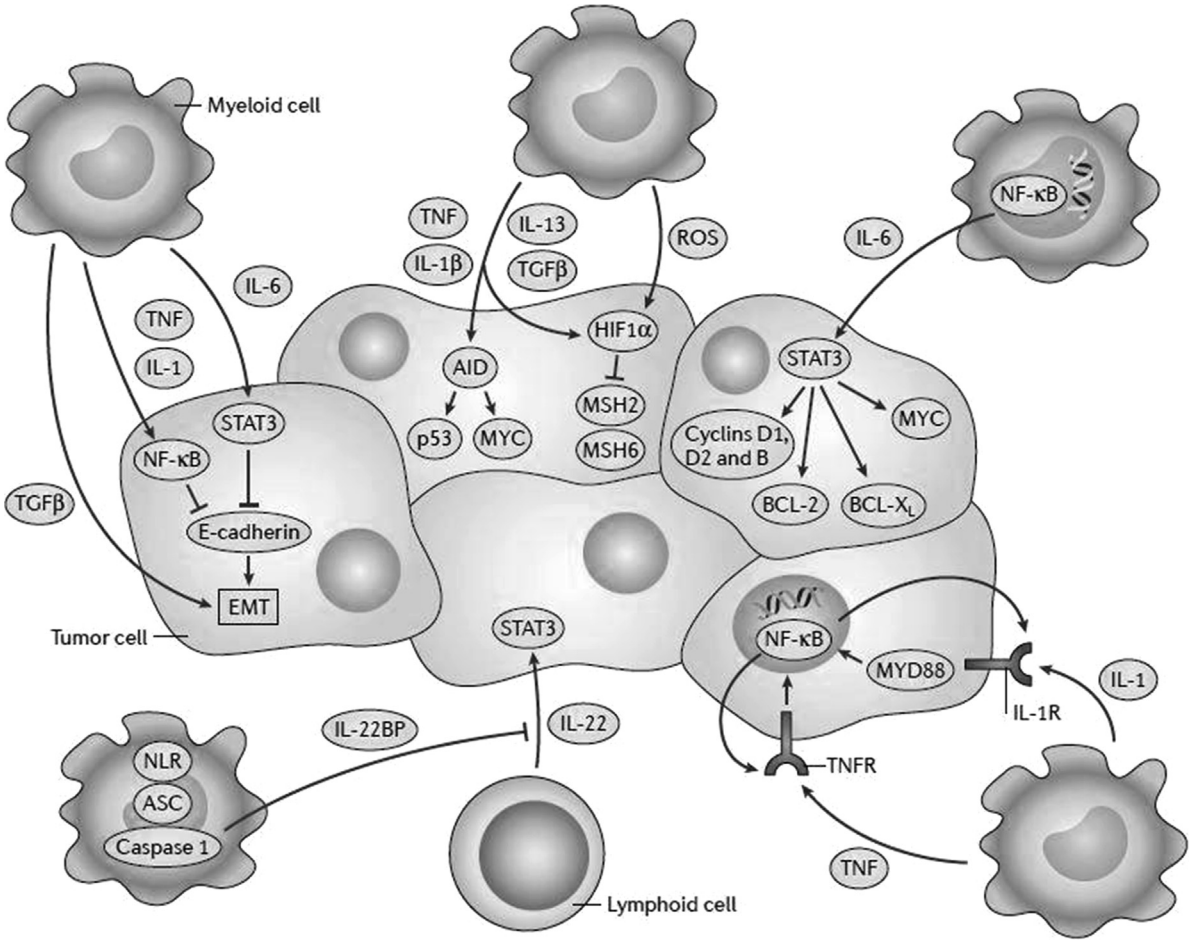

Fig. 1. Inflammatory signaling and carcinogenesis. Pro-inflammatory cytokines induce signal transducer and activator of transcription 3 (STAT3) and nuclear factor-κB (NF-κB) signaling in cancer cells, which leads to the suppression of apoptosis and the promotion of cell cycle progression. Inflammasome-dependent interleukin-22 binding protein (IL-22BP) secretion inhibits IL-22-driven STAT3 induction. Genomic destabilization can be promoted by cytokine-mediated ectopic expression of activation-induced cytidine deaminase (AID) and by hypoxia-dependent suppression of DNA repair mechanisms. In addition, STAT3 and NF-κB signaling also induces epithelial–mesenchymal transition (EMT) by down-regulating the expression of epithelial differentiation markers. ASC, apoptosis-associated speck-like protein containing a CARD; HIF1α, hypoxia-inducible factor 1α; IL-1R, IL-1 receptor; MYD88, myeloid differentiation primary response 88; NLR, NOD-like receptor; ROS, reactive oxygen species; TGFβ, transforming growth factor-β; TNF, tumor necrosis factor; TNFR, TNF receptor.
Reproduced with permission from Elinav et al. (2013).

may be a protective mechanism to avoid NK cell lysis in the case of the down-regulation of MHC class I molecules, as shown in other tumors (Ibrahim et al., 2001; Paul et al., 1998). MHC class II was found to be present in only a small portion of malignant endometrial cells. The scant presence of both the classical MHC I and II molecules in addition to the up-regulation of the non-classical HLA-G indicate the poor antigen-presenting capacity of endometrial tumor cells (Lazaris et al., 2004; Tamiolakis et al., 2005). Cells in the underlying stroma, however, do show MHC II positivity (Lazaris et al., 2004). Taken together, normal endometrial cells can present antigens in the context of MHC molecules, probably as a defense mechanism to pathogens. Endometrial tumor cells, however, down-regulate the expression of MHC molecules to mediate immune escape.

Last, several members of the B7-H family have been described. We recently described the presence of these molecules in both normal endometrium and uterine tumors (Vanderstraeten et al., 2014). We found expression of PD-L1 (B7-H1), and B7-H4 in the vast majority of normal endometria, while PD-L2 (B7-DC) was present in approximately half of normal endometria, albeit at low levels. All of these molecules were also present in endometrial cancer (Vanderstraeten et al., 2014). When comparing the expression levels of all molecules, we did not find up-regulation in endometrial tumors. Although the population investigated was fairly small for a sound analysis, a trend toward decreased survival was found in PD-L1^{+} tumors (Vanderstraeten et al., 2014). Our results on B7-H4 are contradictory to those of a previously published study, in which B7-H4 was reported to be significantly up-regulated in endometrial tumors (Miyatake et al., 2007; Qian et al., 2011). The expression pattern of this molecule was mainly cytoplasmic in conjunction with strong circumferential staining and has been shown to negatively correlate with the number of TIL, both the T cell population as a whole

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($CD3^+$) and the separate CTL population ($CD8^+$) (Miyatake et al., 2007). For the latter, this correlation was also found for B7-H3 (Brunner et al., 2012). These data indicate that, since for most of these mediators no up-regulation was found in endometrial tumors, these molecules may also exert their immunosuppressive functions in both the normal and the cancerous situation, as described above for IDO.

2.2. Infiltration by immune cells

Apart from the mediators just discussed, which can attract immune cells, immune cells themselves are present as part of endometrial tissue. The exact nature of the immune cells present in endometrial tissue/tumors and their function will be elaborated on below. A schematic representation of the presence of immune cells in normal endometrium is given in Fig. 2A and the main players in the tumor microenvironment are depicted in Fig. 2B. Table 1 gives a concise overview of the immunological players in endometrium and endometrial tumors and their implications for tumor biology.

2.2.1. Innate immune cells

Macrophages represent approximately 10% of the total cellular population of the endometrium. They are mostly present in the endometrial stroma and myometrial connective tissue (Wira et al., 2005a). Their frequency is highest before menstruation, as is the frequency of neutrophils. The latter plays a role in the breakdown of the endometrial tissue at menstruation and in the elevation of immune protection during the disruption of the protective barrier of the endometrial epithelium (Hickey et al., 2011). Macrophages play a paradoxical role in cancer, in a sense that they can have both a pro- and anti-tumorigenic function (Ohno et al., 2004). Tumor-associated macrophages (TAM) located in the focal necrotic center of the tumor and TAM at the tumor margin correlated with disease progression and with clinicopathological features of the tumor (Ohno et al., 2004; Soeda et al., 2008). TAM at the tumor margin were associated with the formation of lymph node metastases, indicating tumor progression, whereas macrophages in the tumor nest, the bulky area of the tumor surrounding the tumor center, were associated with better, relapse-free survival. This may be explained by local factors within the tumor, exerting different functions on macrophages. The tumor center, for example, is known to be hypoxic. This is suggested to trigger the angiogenic capacities of macrophages, leading to renewed oxygen supply and tumor progression (Ohno et al., 2004). Another cell type, such as macrophages derived from the myeloid lineage, are myeloid-derived suppressor cells (MDSC). To date, to our knowledge, MDSC have only been described in endometrial cancer by our own group (Vanderstraeten et al., 2014). MDSC analysis was subdivided into the presence of monocytic MDSC ($lin^-HLA\text{-}DR^{-/lo}CD11b^+CD14^+$) and granulocytic MDSC ($lin^-HLA\text{-}DR^{-/lo}CD11b^+CD14^-$). MDSC of both the monocytic and granulocytic types were found, although most of the population identified were of the granulocytic type. This subtype has been described to have the strongest suppressive capacity compared to the monocytic subtype (Raber et al., 2014), providing evidence of increased immunosuppression in endometrial tumors.

The largest representative of the innate immune system, however, is natural killer cells (NK cells). As for the cells described above, their numbers in normal endometrium vary depending on the phase in the cycle. The highest number of NK cells is found in the secretory phase of the cycle. At this point NK cells represent about 70% of the total leukocyte population (Wira et al., 2005a). This is likely the result of both increased IL-15 levels in the endometrium in the secretory phase and of an increased NK cell influx from peripheral blood (Lobo et al., 2004). However, research by Manaster et al. showed that the percentage of NK cells remains relatively constant at approximately 30% of the total lymphocyte population (Manaster et al., 2008). Male et al. found precursor NK cells, so-called stage 3 NK cells in uterine mucosa, in addition to mature, stage 4, NK cells (Male et al., 2010). The authors postulate that stage 3 NK cells ($CD34^-CD117^+CD94^+$) migrate into the uterus where they mature to obtain their distinct phenotype ($CD34^-CD117^{-/+}CD94^+$) (Male et al., 2010). Uterine NK cells are different from their counterparts in blood (Yang et al., 2011). Like NK cells in blood, they express CD94, CD56, and CD9, but do not express CD16, CD8 or CD57. In addition, CD56 is expressed at about ten-fold higher levels in uterine NK cells than in blood NK cells (Yang et al., 2011). Little has been described concerning the functional differences of peripheral blood NK cells and uterine NK cells. NK cells in both proliferative and secretory phase endometrium have been shown to be inert cells that lack both their cytotoxic capacity and their ability to secrete cytokines. However, this can be reverted when the cells are cultured in the presence of IL-15 (Manaster et al., 2008). Stimulation with IL-15 resulted in the up-regulation of the activating NK cell receptors, NKp30 and NKp44, but no difference in the expression of NKp46 and NKG2D was found. In addition, IL-15 activated endometrial NK cells showed increased *in vitro* cytotoxic capability and secreted IP-10 (CXCL-10) and IFN-γ (Manaster et al., 2008). Uterine NK cells are thus suggested to be inert lymphocytes without the cytotoxic capabilities of peripheral NK cells. These NK cells are inactive during the normal menstrual cycle and are suggested to mature to fully functional NK cells during pregnancy (Manaster et al., 2008). There are only a few studies focusing on NK cells in endometrial carcinoma patients. NK cell activity in peripheral blood against K562 cells was found to decrease with an increase in histological differentiation grade and myometrial invasion in early stage (stage I) endometrial carcinoma (Garzetti et al., 1994). A study already published in 1987 by Timonen et al. in eight endometrial cancer patients and one endometrial stromal sarcoma patient showed that unstimulated peripheral blood lymphocytes show cytotoxic responses against autologous tumor and against HeLa cells in seven out of nine patients (Timonen et al., 1987). This activity was increased upon the addition of recombinant IL-2. The IL-2-activated lytic precursor cells belong to the subpopulation of lymphocytes that includes NK cells (Timonen et al., 1987). Ferguson et al. found that NK cells were virtually absent in endometrial tumors (Ferguson et al., 1985). Intratumoral NK cells were

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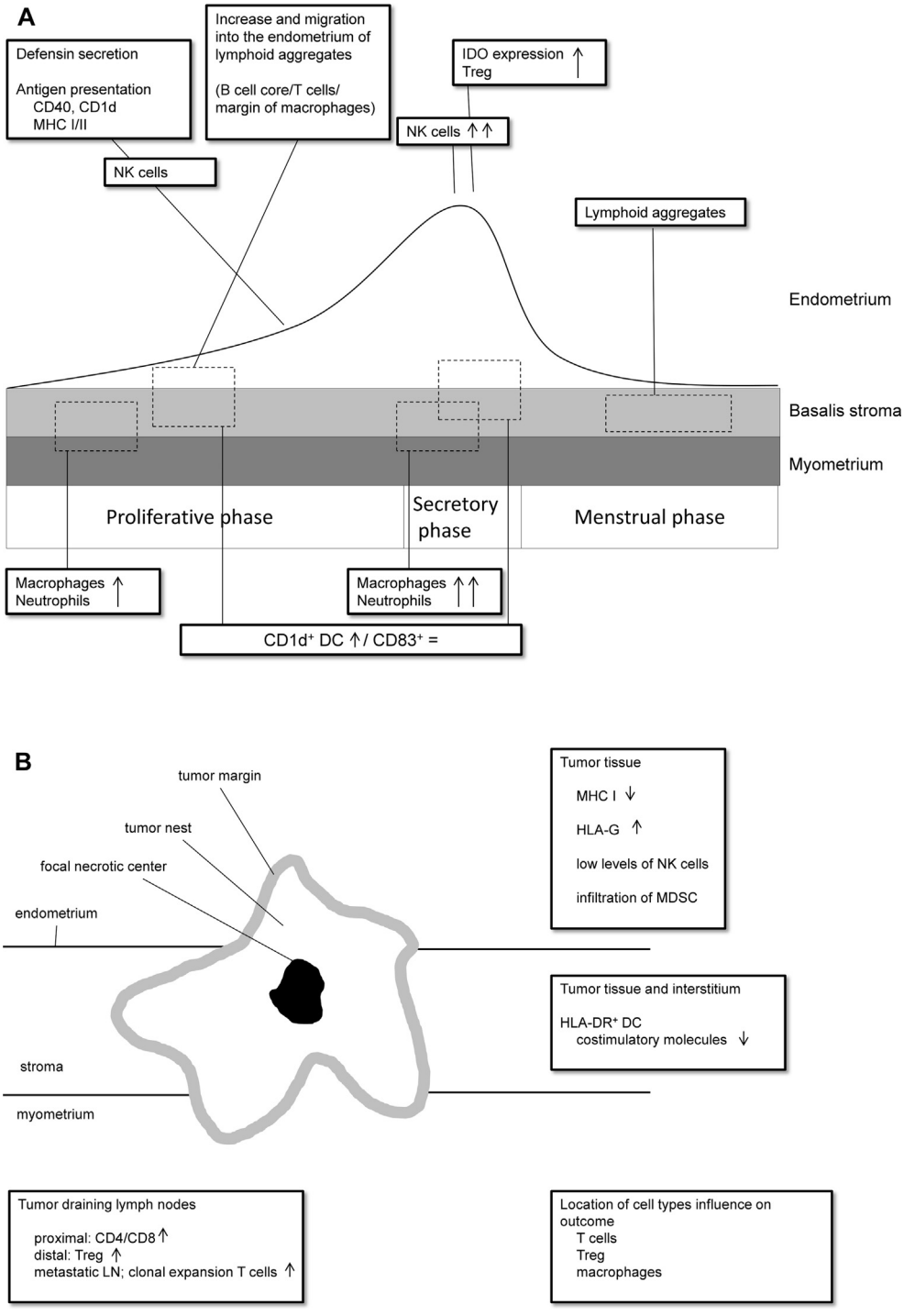

Fig. 2. The immune system in the normal uterus and in uterine cancer. (A) Fluctuations in the immune system in the normal menstrual cycle. During the proliferative phase up until the secretory phase, NK cells and macrophages proliferate and the lymphoid aggregates increase in size. The increased frequencies corroborate their function in the breakdown of the endometrium. $CD1d^+$ dendritic cells (DC) increase in frequency, while $CD83^+$ DC remains constant, possibly indicating DC migration. During the secretory phase, both indoleamine 2,3-dioxygenase (IDO) and the frequency of Treg are increased to create an immunosuppressive environment for possible embryonal implantation. Dashed rectangles indicate the location of the endometrium in which the cells reside. (B) The immune system in endometrial cancer. In contrast to the situation in normal endometrium, major histocompatibility complex (MHC) class I/II molecules are down-regulated, facilitating immune escape, while human leukocyte antigen G (HLA-G) is up-regulated. In addition, myeloid-derived suppressor cell (MDSC) infiltrates are described in uterine tumors and DC have been shown to down-regulate costimulatory molecules. For T cells (including Treg) and macrophages, their exact function and the resulting effect on outcome are dependent on the location within the tumor/at the tumor margin.

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Table 1
Overview of immunological mediators in uterine tumors.

Molecule/cell type	Normal endometrium	Uterine tumors		
		Available data	Correlation with clinicopathology	Relation to prognosis
MHC class I	Expressed	Down-regulated	Down-regulated in advanced and undifferentiated tumors	Worse prognosis
MHC class II	Expressed in ~50% of cases	Present in minority of tumor cells		
HLA-G	Conflicting data	Up-regulated		
IDO	Up-regulated in secretory phase	Up-regulated	Associated with myometrial invasion, lymph node metastases and lymphovascular space involvement	Associated with poor survival
NK cells	Increase during menstrual cycle	Low levels, increased upon progestin treatment	Activity decreased in advanced disease	
Macrophages	Increase during menstrual cycle	Location-dependent pro- or anti-tumor effects	Location-dependent	Location-dependent
Neutrophils	Increase during menstrual cycle	Increased	Increased NLR associated with lymph node metastasis	
DC	Low levels	Increased	Negatively correlated with the clinical stage and lymph node metastasis	
B cells	Present in aggregates			
T cells	Present in aggregates	Conflicting data		Dependent on location and phenotype
Treg	Increase during menstrual cycle	Increased compared with blood	Increased in advanced disease	Worse prognosis
MDSC	Unknown	Present with higher frequency of granulocytic subtype		Unknown

MHC: major histocompatibility complex, HLA-G: human leukocyte antigen G, IDO: indoleamine 2,3-dioxygenase, NK: natural killer, DC: dendritic cells, Treg: regulatory T cells, MDSC: myeloid-derived suppressor cells, NLR: neutrophil to lymphocyte ratio.

analyzed immunohistochemically in endometrial carcinoma patients following progestin treatment (Witkiewicz et al., 2010). After treatment with progestin, the total cytotoxic (granzyme B^+) lymphocyte population in the tumors increased 6.5-fold. While $CD56^+$ NK cells were present in low numbers or absent pre-treatment, the NK cell frequency rose to 76% of the total cytotoxic (granzyme B^+) cell population in endometrial lesions, which showed signs of regression. On the contrary, in lesions of a stable or progressive nature, no increase in NK cells was noted. $CD8^+$ CTL showed a mild increase in regressing lesions, while they remained approximately constant in stable or progressive lesions. Thus, progestin treatment can attract NK cells into uterine tumors, which is associated with disease improvement. In addition, these findings can explain the increased level of NK cells in the secretory phase of normal endometrium, when progesterone levels are highest.

Dendritic cells (DC) were also described in the human endometrium, at relatively low levels compared with other immune cells (Schulke et al., 2008). Throughout the cycle, these cells reside both in the functional and the basal layers. The frequency of immature $CD1a^+$ DC increases during the cycle, while the mature $CD83^+$ DC population remains relatively constant. This indicates that, in accordance with their natural function, mature dendritic cells migrate from their resident tissue. In uterine tumors, $HLA\text{-}DR^+$ DC have been shown to be present in both the glandular cells and the interstitial tissue (Lijun et al., 2012). The functional capacity of tumor-infiltrating DC, however, has been shown to be compromised in uterine tumors, owing to the significantly reduced expression of the costimulatory molecules CD86, CD80, and CD40 compared with DC in normal endometrium (Jia et al., 2012).

2.2.2. Adaptive immune cells

T and B cells, both members of the adaptive immune system, can also be found in the normal endometrium. They are present in uterine mucosa as unique aggregates consisting of a B cell core surrounded by T cells. Additionally, these structures are surrounded by a capsule of macrophages and monocytes (Yeaman et al., 1997). These structures have been suggested to be similar to the mucosa-associated lymphoid tissue (MALT), which can be found in the gastrointestinal system (Marshall and Jones, 1988). The T cells present in these aggregates are almost exclusively $CD8^+$ $CD45RO^+$, indicating that they are memory type effector cells (Yeaman et al., 2001). These aggregates have been shown to increase in size from the proliferative phase, at this point without the B cell core, until the secretory phase of the menstrual cycle. In addition, they are absent in the

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menopause, indicating that their expansion is hormone-driven (Yeaman et al., 1997). This is further exemplified by the observation that T cells within the aggregate express estrogen receptors (Tabibzadeh and Satyaswaroop, 1989). Additionally, Yeaman et al. have shown that the accumulation of T cells is the result of T cell migration toward the endometrium, rather than a proliferation of single resident T cell clones (Yeaman et al., 2001).

The function of these aggregates is largely unknown. However, they may serve a purpose in both the creation of an immunosuppressive environment to allow feto-maternal tolerance on the one hand and on the other hand to create an environment that protects against pathogens during menstruation, when the epithelial barrier is disrupted. The former is exemplified by the observation that the cytotoxic T lymphocytes in the proliferative phase of the cycle have cytotoxic capacity, while this function is severely dampened in the secretory phase, during which conception can occur (White et al., 1997). In addition, $CD8^+$ T cells are still capable of exerting their full cytotoxic function, further indicating that during the secretory phase of the menstrual cycle, a temporary state of immunosuppression occurs to allow possible embryonic implantation. The difference in the cytotoxic capacity of T cells during the different phases of the menstrual cycle is subject to hormonal control to maintain the balance between immune protection and tolerance (White et al., 1997). The latter function of the lymphoid aggregates is supported by the location from which they originate. During the proliferative phase, the aggregates expand from within the basalis stroma, the inner third of the endometrium that is not shed during menstruation. Consequently, the lymphoid aggregates may provide immune protection against pathogens during menstruation. Alternatively, the presence of these aggregates in the basalis stroma may be a means of preventing the loss of T and B cells during menstruation (Yeaman et al., 1997). This type of lymphoid structures, recently termed tertiary lymphoid structures, resemble the MALT found in the gastrointestinal system, as mentioned above. These structures have been described in several tumor types, such as colorectal cancer, lung cancer, melanoma, ovarian cancer, renal cell cancer, and breast cancer (Goc et al., 2013). The co-localization of both T and B lymphocytes in these aggregates has been shown to correlate with improved patient survival (Nielsen and Nelson, 2012). In uterine tumors, MALT-like structures have not been described to date, but tumor-infiltrating lymphocytes (TIL) have been shown in different studies. Chang et al. found that $CD8^+$ TIL showed less expression of granzyme B and perforin than their blood counterparts, indicating possible functional defects or tumor-induced suppression (Chang et al., 2010). However, *in vitro* activation of TIL resulted in adequate activation of TIL and induction to the same polarization profile as found in peripheral blood (*i.e.*, main polarization to Th1-type cells). TIL have been associated with prognosis in endometrial cancer, with contradictory reports. The prognostic value of this infiltrate depends on the location within the tumor. Increased numbers of TIL, of unspecified composition, at the invasive margin of the tumor (*i.e.*, the tumor–myometrial junction) did not have a beneficial effect on patient survival according to a study by Silverberg et al. (1982). These results were contradicted by Kondratiev et al., who found that, although confirming the presence of $CD8^+$ TIL at the tumor-invasive margin, the presence of these TIL was associated with improved prognosis (Kondratiev et al., 2004). However, the latter study only considered $CD8^+$ TIL at the invasive border, while Silverberg et al. considered the total lymphocyte population, which may explain these different findings. Two additional studies investigated the total lymphocyte population at the invasive margin (Ambros and Kurman, 1992; Deligdisch, 1982). Deligdisch observed that the presence of an infiltrate consisting of lymphocytes and plasma cells, potentially indicating the described tertiary lymphoid structures, appeared to be related to low-grade endometrial tumors, and suggested that TIL might be associated with a favorable prognosis (Deligdisch, 1982). A later study by Ambros and Kurman refuted this suggested association (Ambros and Kurman, 1992). Intratumoral $CD8^+$ TIL have been associated with improved disease-free survival in both type I and type II endometrial cancer (de Jong et al., 2009). These intratumoral TIL were found more frequently in low-grade tumors than in high-grade tumors. The presence of $CD45RO^+$ T cells, indicating memory T cells, was also shown. Moreover, the presence of memory T cells was associated with increased overall survival and with reduced events of recurrence (de Jong et al., 2009). Chang et al. described the majority of tumor-infiltrating $CD8^+$ T cells as being $CD28^-CD45RA^-CD45RO^+$, defining terminally differentiated T cells. In addition, the T cells appeared to be in an activated state, exemplified by the expression of CD69, CD103, and CD152 (Chang et al., 2010). In the proximal tumor-draining lymph nodes (TDLN), the CD4/CD8 ratio is increased (Fattorossi et al., 2004). In addition, Yamamoto et al. found that clonally expanded T cells are absent from TDLN in patients with local endometrial tumors, while clonally expanded T cells could be retrieved from TDLN and peripheral blood in patients suffering from metastatic cancer, supporting the role of immune responses to solid tumors (Yamamoto et al., 1995). This specific appearance of T cell clones in the TDLN of metastatic tumors may be a consequence of direct T cell priming by (metastasized) tumor cells present in the TDLN in metastatic tumors. This results in the expansion of T cell clones in the affected lymph nodes. This direct priming does not occur in unaffected lymph nodes, as is the case in early-stage disease (Contassot et al., 2009). The results of Yamamoto et al. expand the earlier findings of Garzetti et al. (1995), who did not find any clinical significance in the lymphocyte distribution in lymph nodes in patients with early-stage disease. In addition, Garzetti et al. showed that myometrial invasion with or without lymphovascular space involvement was associated with increased $CD16^+$ and $CD56^+$ cells, defining NK cells, in pelvic nodes (Garzetti et al., 1995).

Regulatory T cells (Treg) have a natural function to suppress ongoing immune responses when they are no longer necessary. However, this may also cause suppression of an antitumor immune response. Treg have been shown to be increased in the peripheral blood of normal controls in the late follicular phase (Arruvito et al., 2007). Analysis of the Treg frequency in the endometrium showed that Treg are only infrequently present in the endometrium and that

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their frequency is higher in the proliferative phase than in the secretory phase (El-Hamarneh et al., 2013). Collectively, these data indicate that the frequency of Treg cells appears to increase during the proliferative phase and is reduced after ovulation.

Several studies have reported the presence of Treg in endometrial carcinoma. Intratumoral Treg are increased compared with peripheral blood (Chang et al., 2010). In this particular study it was also shown that, like CTL, intratumoral Treg also express granzyme B, indicating the capacity to lyse effector cells. However, Treg in stromal tissue were found to be significantly lower in tumor than in normal endometrium (Giatromanolaki et al., 2008). Although lower, high tumoral Treg counts were shown to correlate with increased vascularity (Giatromanolaki et al., 2008), tumor grade, stage, the extent of lymph node metastases and myometrial invasion (Chang et al., 2010) in addition to worse disease-free survival (Yamagami et al., 2011). The latter has also been shown to result from the presence of high Treg/CD8 and Treg/CD4 ratios (Yamagami et al., 2011). In distal TDLN, the proportion of functional regulatory T cells is increased (Fattorossi et al., 2004).

Taken together, the fluctuations of the different immunological cell types during the normal menstrual cycle are a further indication of the dual role the immune system plays in the uterus, as described earlier. The immunosuppressive capacity that certain cell types, such as Treg, have within the framework of feto-maternal tolerance also contributes to immune escape by tumors. Some cell types, such as macrophages and T cells, appear to have a different effect on the outcome of a tumor, depending on the location in which they reside. This likely indicates that at different sites within the tumor or the tumor microenvironment the immune system may be differentially influenced in such a way that the functional capacities of the immune cells are influenced toward either an anti-tumor or a pro-tumor profile.

3. Clinical implications

The currently reviewed data provide an insight into several immune mechanisms in uterine tumors and indicate possible options for therapeutic modalities. The composition of the intratumoral immune infiltrate may have an important influence on treatment outcome. This phenomenon has recently been described in ovarian cancer (Zhang et al., 2003). It was shown that the five-year survival rate of ovarian cancer patients who underwent debulking surgery and received adjuvant chemotherapy was at least six times higher in patients with an intratumoral T cell infiltrate in the tumor islet, compared with patients without a T cell infiltrate (Zhang et al., 2003). Therefore, strategies could be developed to skew the unfavorable immune infiltrate in certain patients into a more immunogenic microenvironment to enhance the efficacy of conventional treatment in these patients. Several negative immune regulators are present and possibly active in endometrial cancer. Of the currently reviewed regulators, several could present as valuable targets for therapeutic intervention. First, IDO and PD-L2 are useful targets, although only in a limited percentage of tumors (Vanderstraeten et al., 2014). Several trials are currently ongoing to evaluate the use of IDO inhibitor 1-methyltryptophan (registered at www.clinicaltrials.gov). No studies were listed to evaluate the use of an IDO inhibitor in endometrial cancer. Several trials are currently ongoing to evaluate its use, either in combination with other treatments for ovarian cancer and peritoneal tumors or alone. Both PD-L1 and B7-H4 could represent targets in EMCAR, because of their high expression levels. Antibodies directed against PD-L1, or the receptor PD-1, are being used in trials for several solid tumors. Anti PD-L1 treatment resulted in objective response rates ranging from 6% to 17% in patients with solid tumors, including melanoma, renal cell carcinoma, and non-small cell lung cancer, while anti-PD-1 led to objective response rates of up to 27% (Brahmer et al., 2012; Topalian et al., 2012). MDSC also represent a valuable target in endometrial cancer. Preliminary data of a clinical trial evaluating MDSC targeting with the use of all trans-retinoic acid (ATRA) showed promising results. In small cell lung cancer patients, co-treatment with a DC vaccine and ATRA resulted in a substantial increase in immune response after vaccination, as exemplified by an increase in IFN-γ-secreting antigen-specific T cells (Iclozan et al., 2013).

Last, the presence of NK cells in uterine tumors correlates with a beneficial treatment outcome in uterine tumors. This provides motivation for the use of adoptive NK cell therapy in uterine tumors, which remains to be explored.

4. Conclusion

The data outlined here clearly show that the immune system is present and active in both normal endometrium and endometrial tumors. In the normal endometrium, the immune system plays a central role in protection against pathogens and in safeguarding feto-maternal tolerance. Like this dual role in a healthy situation, it also has both a pro- and anti-tumorigenic function. In our opinion, the interplay between positive and negative players and mechanisms in tumor development and progression provides possible intervention options in the treatment of endometrial cancer, which deserves further attention in future research.

Conflict of interest

The authors state to have no financial or commercial conflict of interest.

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